

DETAILED ACTION

The amendment filed 01 April 2011 has been received, entered and carefully considered.

The following information has been made of record in the instant amendment:

1. Claims 9-11 and 20-22 have been canceled. These claims were cancelled in the amendment filed previously.
2. Claims 1 and 13 have been amended to delete the term filtered.
3. Remarks drawn to rejections under 35 USC 112, second paragraph and 103(a).
Claims 1-8, 12-19 and 23-32 are pending in the case.

The following are new ground(s) or modified rejections necessitated by Applicant's amendment, filed 01 April 2011, where the limitations in pending claims 1 and 13 as amended now have been changed. Specifically, in claims 1 and 13 the term 'filtered' has been deleted. Therefore, rejections from the previous Office Action, dated 01 December 2010, have been modified and are presented below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1-6, 8, 12-17, 19 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the step of filtering out any undissolved particles, originally recited as step (c). It is known in the art that undissolved

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particles can interfere and prevent crystallization of the desired product. Applicants have to insert the recitation “the step of filtering out any undissolved particles” in claims 1 and 13.

Claims 2-6, 12, 13-17, 19 and 23 which depend from a rejected base claim that is incomplete for omitting essential elements, such omission amounting to a gap between the elements are also rejected for the same reasons.

Response to Applicants Arguments

Applicants have traversed the above rejection arguing that:

1. Although it is known that filtration is beneficial it is also recognized that it is not a requirement. In some crystallizations seed crystals are added to accelerate the process. They are particulate matters that serve as nucleation.

2. Further, Advanced Practical Organic chemistry, 1995, page 185, paragraph 3 (this reference has not been provided to the Office) it is stated that filtering the hot solution to remove insoluble impurities is often problematic and should not be carried out unless an unacceptable amount of insoluble material is suspended in solution. Hence it is understood that filtration is not a requirement.

Applicants’ arguments have been considered but are not found to be persuasive.

Seed crystals are added to induce crystallization. But the crystals added are those of the compound that is being crystallized. They are different from other insoluble impurities and do not interfere with crystal formation. The filtration of the hot solution to remove impurities is not as problematic as stated in the cited reference. One of ordinary skill in the art knows that other than the hot solution the filter funnel with filter paper and the container into which the solution is

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being filtered have to be kept warm so that rapid crystallization does not occur. One of ordinary skill in the art also known that even a very small amount of impurity can interfere with crystallization. Even if the compound crystallizes without the insoluble impurities being filtered out the resulting crystals are going to have the impurities still present in the crystallized product rendering it still impure and defeating the purpose of crystallization. For this reason the artisan knows that it is important to carry out the filtration step. The rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

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the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8, 12-19 and 23-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Farag et al (Bull. Pharm. Sci. Assiut University, 1998, 21(1), 1-6, of record) and Feldman et al (Phytochemistry, 1999, 51, 867-72, of record), in view of Pfeffer et al (US 4,107,425, of record), Experimental Organic Reactions (1957, 18, pages 504-505, English Translation, of record) and Ault (Techniques and Experiments for Organic Chemistry, 1987, pages 44-46, of record and pages 120-21, of record).

Farag et al teach the extraction and separation of the alpha and beta anomers of pentagalloyl glucose (PGG) existing as a mixture in a methanol extract. From this extract the individual alpha and beta isomers have been separated via chromatography using 2:1 water and methanol as solvents (page 2, left col., see Extraction and Fractionation; Isolation and compounds 3 and 4 on the right column). The major component is water. This indicates that there is a difference in solubility of the alpha and beta anomers of PGG in water and this can be taken advantage of for separation of the two anomers from a solution containing a mixture of the two anomers in water.

Feldman et al teach that the individual alpha and beta anomers of PGG is separated and purified for binding studies for each anomer (page 869, Table 1).

Farag et al. and Feldman et al do not specifically teach the separation of the alpha and beta anomers of pentagalloylglucose (PGG) from a mixture of the alpha and beta anomers using either water (instant claim 1) or acetone (instant claim 13) via crystallization as instantly

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claimed. However, according to the teaching of Farag and Feldman, the separation of the alpha and beta anomers of PGG is not only known in the art, but also alpha and beta anomers are known to have different properties and activities.

Pfeffer et al. teaches that using crystallization for the separation of the beta anomer of tetra-O-benzyl-1-hexadecanoyl-D-glucose from a mixture comprising an 11:89 ratio of the alpha and beta anomers, via crystallization from absolute ethanol (col. 5, line 45 through col. 6, line 13) is known in the art. This is separation of a single anomer (the beta anomer) from a mixture comprising 50% or more of the beta isomer and less than 50% of the alpha isomer as in instant claim 13. The steps used by Pfeffer are the same as recited in steps (a)-(c) in claims 1 and 13 and steps (a)-(d) in claims 24 and 27. One of ordinary skill in the art would use these same steps for the separation of the individual anomers of PGG via crystallization.

According to Experimental Organic Reactions (English translation of section 3.2) resolution of racemic modification (separation of anomers/optical isomers) can occur via recrystallization. Examples wherein water/methanol or acetone is used to separate racemates are disclosed (Translation, page 1, second paragraph). This means that alpha and beta anomers of PGG can also be separated via crystallization from a mixture using water and acetone as solvents based on the differences in solubility of the anomers as seen in the teaching of Farag et al and such separation via crystallization of closely related derivatives as taught by Pfeffer.

According to Ault (Techniques and Experiments for Organic Chemistry, 1987, pages 120-21) the separation of compounds is based on the ability of the solvent used to selectively dissolve a substance that is to be separated (page 120, last paragraph). Separation depends on the difference in solvent power towards the substances (page 121, first two lines below Table). This

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indicates that the difference in solubility of substances in a solvent can be used for separating a mixture via crystallization also. In the instant case such a difference is seen in the teaching of Farag et al for the alpha and beta anomers of PGG. Based on the teaching of Farag, Pfeiffer and Ault a reasonable expectation of success is seen for separating the alpha and beta anomer of PGG using water and acetone as solvents.

At pages 44-46 Ault teaches that in the process of crystallization of a solid from a solvent, the compound is dissolved in the solvent and the resulting solution is filtered to remove undissolved material (page 46, Fig. 8.1; steps recited in claims 30-31). This is a step that is used in all crystallizations wherein undissolved material is present. Hence, one of ordinary skill in the art would use this step in the instant process if undissolved material is present. One of ordinary skill in the art knows well that such undissolved material if not removed before the cooling step could prevent the desired compound from crystallizing out of solution. Ault also teaches that after the compound is added to the solvent it should be warmed up if necessary to dissolve it completely in the solvent (page 46, last paragraph). This is same as the steps recited in instant claims 5-6, 8, 16-17 and 19. Therefore, based on the teaching of the prior art above the separation of the alpha and beta isomers of PGG using the solvents as instantly claimed is predictable and one of ordinary skill in the art would use recrystallization to separate the anomers.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to separate the alpha and beta anomers of penta-O-galloyl-D-glucose from a mixture of the alpha and beta anomers via the method as instantly claimed since analogous separations of the alpha and beta anomers of glucose derivative structurally similar to pentagalloyl glucose via

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crystallization using water/methanol or acetone as solvents have been disclosed in the prior art. Therefore the prior art shows that it is possible to separate the alpha and beta anomers of the pentagalloyl derivative of glucose.

One of ordinary skill in the art would be motivated to use the method as instantly claimed since separation of anomers via crystallization is a well known technique and as disclosed in the art readily available solvents like water and acetone have been successfully used for such separations. One of ordinary skill in the art would expect the separation of the alpha and beta galloyl derivatives of glucose to also take place with a reasonable expectation of success based on the disclosure of the prior art.

MPEP 2141 states, "The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in KSR noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Court quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), stated that "[R]ejections on obviousness cannot be sustained by mere conclusatory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." KSR, 550 U.S. at ,82 USPQ2d at 1396.

Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) " Obvious to try " choosing from a finite number of identified, predictable

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solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

Rationales (A), (C) and (E) are applicable in this case. The prior art teaches the use of water and acetone for separating components from a mixture via crystallization using these two solvents, which are also used in the instant method. In the instant case separation of the alpha and beta anomers by choosing a known method (crystallization) and choosing a solvent for crystallization from a finite number of choices disclosed in the prior art with a reasonable expectation of success, according to KSR renders the instant claims obvious. Also the teaching of Farag shows that difference in solubility between two substances (alpha and beta anomers of PGG in the instant case) can also be used to separate them from a mixture via crystallization since difference in solubility is a property known in the art for separating individual components from a mixture via crystallization.

"Aventis Pharma Deutschland v. Lupin Ltd., 499 F.3d 1293 (Fed. Cir. 2007). A chemical compound would have been obvious over a mixture containing that compound as well as other compounds where it was known or the skilled artisan had reason to believe that some desirable property of the mixture was derived in whole or in part from the claimed compound, and separating the claimed compound from the mixture was routine in the art."

In the instant case separating the alpha and beta isomers of PGG is known in the art as explained above.

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It is well within the skill level of the artisan to prepare a single crystal of the respective anomers via the same crystallization technique and using the same solvents from samples that are greater than 95% pure since PGG is known in the art to have beneficial effects (as disclosed in the Background section in the Specification) and one of ordinary skill in the art would use the known separation technique disclosed in the art to separate the isomers in order to look at the activity of the individual isomers. It is also well within the skill level of the artisan to adjust the ratio of the solvent to the product to be crystallized, the duration of cooling to obtain crystals, the type of filter paper to be used for separating the crystals, etc. in order to recover the maximum amount of the pure anomer from the crystallizing solution.

Response to Applicants Arguments

Applicants have traversed the rejection under 35 USC 103(a) of record arguing that:

1. Faraq discloses chromatographic separation of alpha and beta PGG mixtures. Faraq did not use crystallization for the separation. Faraq does not comment on the difference in solubility of the anomers. The separation of the anomers is dependent on the differences in size and affinity and not on solubility.

2. Feldman discloses the separation of benzylated derivatives of alpha and beta PGG. Benzylated anomers possess properties that are different from non-benzylated anomers. For example the molecular weight is different. The benzylated derivatives are non-polar. Alpha and beta PGG are polar.

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3. Pfeffer discloses crystallization of a tetrabenzylated sugar having no free hydroxyl groups. Pfefer's compound has no free hydroxyls, whereas PGG has 15 free hydroxyl groups. Pfeffer also teaches that not all anomers may be separated by crystallization.

4. Experimental Organic Reactions discloses that difficulty and uncertainty are encountered when crystallization is attempted. Success for this method is rare.

Applicants' arguments have been considered but are not found to be persuasive.

Faraq may not disclose the use of crystallization to separate the anomers of PGG. The separation in chromatography is not entirely dependent on size and affinity alone. In the instant case both the anomers of PGG are about the same size and affinity would also be expected to be the same since the only difference is between the two anomers is the orientation of the anomeric substituent. So size and affinity alone cannot contribute to the difference. The difference in solubility in the solvent used also matters. The fact that separation of two almost identical compounds was achieved by Faraq using water as the major component for solvent tells one of ordinary skill in the art that there is a solubility difference between the two anomers in water.

Feldman does not specifically teach that the difference in molecular weight has anything to do with separation via crystallization. The same is true of polarity too. Applicants are just stating differences but are not supporting their claim with additional references or teachings in Feldman that support their position.

Pfeffer teaches separation of the beta anomer of tetra-O-benzyl-1-hexadecanoyl-D-glucose. This compound has an ester group similar to the one in PGG even though it may not be the same. The presence of ether groups may change the properties including the solubility. But

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solubility difference is what is critical for separation of two compounds from a mixture via crystallization.

The teaching regarding the difficulty and uncertainty in crystallization in Experimental Organic Reactions is a general one. If it is that difficult and uncertain then the myriad of organic compounds known in the art to be purified by crystallization would not have been possible. For a process step like crystallization, which has been used in organic chemistry for several decades as a purification method and also as a separation method there is reasonable expectation of success that such a tested method, especially based on the teachings of the art cited, would yield predictable results in the instant method of separation.

Conclusion

Claims 1-8, 12-19 and 23-31 are rejected

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654.

The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ganapathy Krishnan/

Examiner, Art Unit 1623

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